Somatosensory electrical stimulation produces motor learning and synaptic plasticity

Veldman, Menno Pieter

3 DIRECT AND CROSSED EFFECTS OF SOMATOSENSORY ELECTRICAL STIMULATION ON MOTOR LEARNING AND NEURONAL PLASTICITY IN HUMANS

Veldman, M.P., Zijdewind, I., Solnik, S., Maffiuletti, N.A., Berghuis, K.M.M., Javet, M., Négyesi, J., Hortobágyi, T.

European Journal of Applied Physiology (2015). 115(12):2505-19

ABSTRACT

Introduction: Sensory input can modify voluntary motor function. We examined whether somatosensory electrical stimulation (SES) added to motor practice (MP) could augment motor learning, interlimb transfer, and whether physiological changes in neuronal excitability underlie these changes. *Methods:* Participants (18-30 y, n=31) received MP, SES, MP+SES, or a Control intervention. Visuomotor practice included 300 trials for 25 minutes with the right-dominant wrist and SES consisted of weak electrical stimulation of the radial and median nerves above the elbow. Single- and double pulse transcranial magnetic stimulation (TMS) metrics were measured in the intervention and non-intervention extensor carpi radialis. *Results:* There was 27% motor learning and 9% (both $p < 0.001$) interlimb transfer in all groups but SES added to MP did not augment learning and transfer. Corticospinal excitability increased after MP and SES when measured at rest but it increased after MP and decreased after SES when measured during contraction. No changes occurred in intracortical inhibition and facilitation. MP did not affect the TMS metrics in the transfer hand. In contrast, corticospinal excitability strongly increased after SES with MP+SES showing sharply opposite of these effects. *Conclusions:* MP and SES each can produce motor learning and interlimb transfer and are likely to be mediated by different mechanisms. The results provide insight into the physiological mechanisms underlying the effects of MP and SES on motor learning and cortical plasticity and show that these mechanisms are likely to be different for the trained and stimulated motor cortex and the non-trained and non-stimulated motor cortex.

3.1 INTRODUCTION

Sensory inputs from the environment provide feedback for the motor system to accurately perform motor tasks and are essential for motor learning [1,2]. In contrast, reduced sensory function results in decreased manual motor function [3] and interferes with the recovery of voluntary movements after a stroke [4]. These observations led to the idea that enriched compared with normal sensory inputs could augment motor performance. Indeed, several studies reported increases in performance after mild, low-intensity peripheral nerve stimulation, i.e., somatosensory electrical stimulation (SES), but almost exclusively in patients with neurological disorders [5-10].

The mechanisms of how SES improves motor performance and if it could have non-focal crossed effects are not entirely clear. Neuroanatomical, imaging, neuromagnetic, and electrophysiological studies revealed increased activation of the contralateral primary sensory cortex (S1), supplementary motor area, dorsal premotor cortex, posterior parietal cortex, and secondary sensory cortices (S2) bilaterally after SES [11-19]. In addition, the excitability of the corticospinal path as evaluated by the amplitude of motor evoked potentials (MEPs) induced by transcranial magnetic stimulation (TMS) increased after bouts of SES in the stimulated [20-25] and homologous contralateral muscles [26], confirming that unilateral SES can have non-focal, bilateral effects.

That motor practice and SES administered individually would activate similar structures, raised the possibility that SES could have an additive effect in the SES-stimulated muscles (i.e., direct effects) when combined with motor practice. That is, SES may upregulate the excitability of neurons also accessed by motor practice because of direct connections between SES-activated sensorimotor areas and the primary motor cortex (M1). To strengthen this hypothesis, motor practice, in addition to SES, also increases corticospinal excitability [27,28]. In addition, it is also possible that due to its bilateral effects on putative sensorimotor areas, SES could have an additive (i.e., crossed effects) effect in the non-stimulated muscles [29]. Therefore, the purpose of the present study was to examine the possibility that SES added to motor practice could augment motor learning, interlimb transfer, and neuronal excitability in healthy adults. To address potential mechanisms underlying the direct, crossed, and additive effects of SES, we measured corticospinal excitability, short-interval intracortical inhibition (SICI), intracortical facilitation (ICF), interhemispheric inhibition (IHI), and contralateral facilitation (CLF) in the left and right M1 by means of TMS.

3.2 MATERIALS AND METHODS

3.2.1 Participants and ethical approval

Thirty-one healthy right-handed volunteers (age 22 ± 3 years, 16 men) agreed to participate in this study. Handedness was determined using the Edinburgh Handedness Inventory [30]. Based on health-related and TMS questionnaires [31], participants had no history of neurological disorders, were not taking drugs that affected functioning of the central nervous system, or had no contraindications for TMS. Every participants included in the

study signed a written informed consent. The experiments were conducted according to the declaration of Helsinki and the Medical Ethical Committee of the University Medical Centre Groningen approved the experimental protocol and the study was registered at the Dutch trial register (NTR4397).

3.2.2 Experimental design

After meeting the inclusion criteria, participants were randomly assigned to one of three intervention groups: motor practice (MP; n = 8; 4 men; 23.6±3yrs; 1.77m; 71.8kg); SES (n = 8; 4 men; 21.9±2yrs; 1.79m; 73.2kg); MP+SES (n = 9; 5 men, 20.7±2yrs; 1.82m; 77kg); or Control (n = 6; 3 men; 22.0±2yrs; 1.75m; 70.8kg) (Figure 3.1). Before the start of the intervention, baseline measures were performed by means of TMS and peripheral electrical nerve stimulation. Familiarization with the motor task consisted of three visuomotor trials with each hand before the behavioral testing started. As a control group to control for testing effects, six participants performed familiarization and behavioral measures without any intervention.

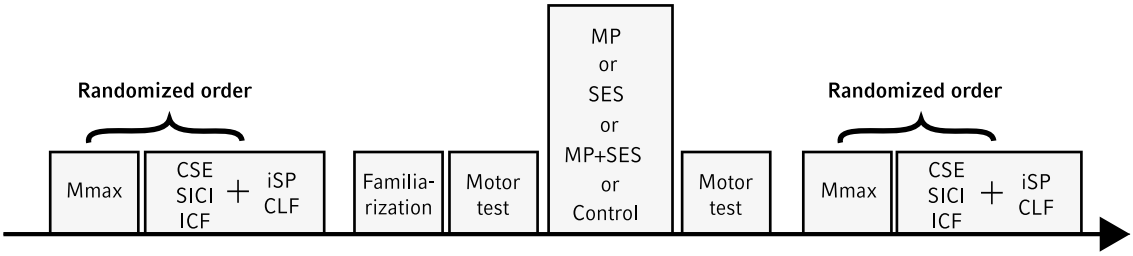

Figure 3.1. *Schematic overview of the experimental design. Baseline measurements including maximal compound action potentials (Mmax), corticospinal excitability (CSE), short-interval intracortical inhibition (SICI), intracortical facilitation (ICF), contralateral facilitation (CLF), and ipsilateral silent period (iSP) were performed before familiarization of the visuomotor task and after completion of one of the three interventions and motor tests.*

3.2.3 Behavioral testing

Performance in the visuomotor task was the behavioral outcome. Participants sat in a chair without armrests, 90 cm in front of a laptop computer's monitor (diagonal dimension 40 cm). With the thumbs superior, participants placed the half-supinated right or left hand inside a padded manipulandum. The center of the wrist joint was aligned with the axis of the manipulandum. The device allowed participants only to flex and extend the wrist in the sagittal plane. The resting hand was placed on the table in a half supinated position, covered with soft material for the comfort of the participants. The feet were on the floor with the knees flexed 90°.

Visuomotor performance was tested using 12 trials before and after each of the three interventions or control period. As in previous studies using the ankle, elbow, and metacarpophalangeal joints, participants followed a preprogrammed template as accurately as possible by flexing and extending their wrist [27,28,32]. Custom software-generated templates appeared in the middle of the monitor's left side in white over a

dark blue background in high resolution. The templates progressed from left to right at a speed of 3.3 to 4.0 cm/s. To make the visuomotor target more challenging to follow, wrist flexion and extension appeared respectively as downward and upward deviation on the monitor. In total, there were six different templates that appeared in random order and duration, varying between four to six seconds, on the screen but each participant received the same set of templates before and after the intervention.

3.2.3.1 MP intervention

MP consisted of 300, 5-s-long visuomotor intervention trials with the right hand that differed from the test trials. Both intervention and test templates had, on average, seven turns (i.e., changes in direction) and varied randomly in duration between four to six seconds. The intervention trials were divided in five blocks of 60 trials, with two minutes of rest between blocks. After every 15 trials, participants were asked to count backwards by seven, starting from a randomly determined two-digit number to keep attention high. To rule out the effects electrodes attached to the skin, two electrodes (ConMed Cleatrode, AG/AgCl, Ref 1720-003, NY, USA) were placed over the radial and median nerve of the right arm above the elbow but no electrical current was applied.

3.2.3.2 SES intervention

Surface electrodes were placed as described for the MP intervention. A constant-current stimulator (Digitimer Ltd model DS7A, Welwyn Garden City, UK) was programmed to deliver 500ms-trains of electrical stimuli continuously, with one train per second (duty cycle: 50%). Each train consisted of five square wave pulses delivered at 10Hz (pulse width, 1ms) [23]. At one millisecond pulse width, sensory fibers have a lower threshold than motor fibers whereas at a shorter pulse width, motor fibers have a lower threshold compared to sensory fibers. Therefore, SES as used in the present study activated predominantly cutaneous and proprioceptive fibers [33]. Stimulus intensity was set at twice the perceptual threshold (2.8 ± 2.1 mA), determined as the lowest stimulation intensity perceived by the participant. Participants in this group sat in front of a table and looked at the computer monitor while receiving stimulation in five blocks of five minutes (1,500 trains and 7,500 pulses in total) and performed the backward counting attention task during which SES was paused. The SES parameters selected for the present study were based on clinical studies that reported increases in motor performance and corticospinal excitability after a period of SES [5,8,10].

3.2.3.3 MP+SES intervention

This group received SES concurrently with MP. The details of this combined MP+SES protocol were identical to the details of the individual MP and SES protocols.

3.2.4 EMG recording

Surface electromyography (EMG) was recorded from the left and the right extensor carpi radialis (ECR) using 37x26x15mm, 14g, wireless, pre-amplified parallel-bar sensors, affixed to the skin with a four-slot adhesive skin interface (Trigno, Delsys Inc, Natick, MA, USA). The EMG signal was recorded with a bandwidth of 20-450 Hz, amplified 909 times, with a channel noise less than 0.75 μV, and a common mode rejection ratio over 80 dB. To minimize noise in the EMG signal, the skin over the muscle belly was shaved,

scrubbed with sandpaper, and cleaned with alcohol. EMG activity was sampled at 4 kHz and EMG signals were recorded using data acquisition software (Power 1401 and Signal, Cambridge Electronics Design, Cambridge, UK). The data were stored on a personal computer for off-line analysis.

3.2.5 Transcranial magnetic brain stimulation

MEPs were evoked by a figure of eight-shaped magnetic coil connected to two Magstim 200 magnetic stimulators through a BiStim module (loop diameter, 9 cm; Magstim, Dyfed, UK). MEPs were obtained in all participants except for one participant in SES and all control participants. The coil was placed over the motor area of the right and left hand with the handle pointing backwards at ~ 45° away from the sagittal plane. The optimal spot, the hotspot to evoke MEPs in the ECR was marked on a cloth cap worn by the participants to ensure consistent repositioning of the coil. Resting motor threshold (rMT) was determined in a sitting position to the nearest 1% of the maximum stimulator output that evoked MEPs in the ECR of at least 50 μV in five out of 10 subsequent stimuli.

Corticospinal excitability, SICI and ICF were measured in one TMS run, delivered in a random order with 10% variation in 5-s-inter-pulse time to reduce anticipation by the participant. To evoke SICI and ICF, a paired-pulse TMS protocol was used as described previously [34]. A subthreshold conditioning stimulus set at 80% of rMT was delivered 2 ms for SICI and 10 ms for ICF before a suprathreshold test stimulus set at 120% of the rMT. In all groups, there were 10 corticospinal excitability, 10 SICI, and 10 ICF trials, delivered with at least five seconds between trials at a constant TMS intensity regardless of changes in excitability [35].

In a separate TMS run, iSP and CLF were measured. First, maximum voluntary contractions in both ECR muscles were determined. With the test stimulus set at 160% of rMT, five TMS pulses were given with both hands at rest. Thereafter, TMS pulses were given to the M1 while the hand ipsilateral to the TMS stimulus hand was contracted at 20% of the maximum voluntary force, evoking an iSP in the contracting hand.

3.2.6 Peripheral electrical nerve stimulation

Maximum compound action potentials (Mmax) were evoked in the left and right ECR by stimulating the radial nerve above the elbow with a single pulse (pulse width, 1ms) by means of the same stimulator used for SES. Stimulation intensity was increased from a subthreshold level to an intensity at which the peak-to-peak amplitude of the M-wave was no longer increasing. An extra pulse at 120% of this intensity was given to ensure a plateau was reached. The purpose of this measurement was to normalize MEPs by Mmax, thus enabling the comparison between pre- and post-intervention measures.

3.2.7 Data analysis

Visuomotor performance was calculated as the mean absolute deviation from the pre-programmed template using a Matlab script (Mathworks, Natick, Massachusetts, USA). To determine if the intervention differently affected the magnitude of learning, the mean absolute error for the 12 pre-intervention trials was compared to the mean absolute error for the 12 post-test trials.

We quantified peak-to-peak amplitude of each MEP recorded in the right and left ECR. MEPs that differed from the mean by more than two standard deviations were excluded for every participant separately. In total, 7% of all MEPs were excluded. We compared Mmax-normalized MEPs before and after the intervention (corticospinal excitability = MEP/Mmax). Conditioned MEPs were expressed as a percent of test MEP size (SICI = conditioned MEP/test MEP; ICF = conditioned MEP/test MEP). Lower values for SICI and ICF represent more inhibition and less facilitation, respectively.

Onset, offset, and duration of iSP were determined using an adjusted version of the Teager-Kaiser Energy Operator [36], detecting disruption in the ongoing EMG activity. This statistical method uses the signal and noise elements and an upper and lower variation limit in the EMG recording ± (MCD × 2.22). MCD represents the mean consecutive difference of pre-stimulus EMG points for each individual. The value 2.22 corresponds to 2.5 times the SD and gives a measure of the 98.7% variation limits of the prestimulus EMG.

CLF was calculated as a ratio between the MEP size during contraction of the hand ipsilateral to the TMS stimulus and MEP size with this hand at rest (CLF = MEP 20%MVC/ MEP rest). Background EMG activity was determined after rectifying the EMG signal. The relation between associated activity in the 'resting' hand and facilitation of the MEP size during contraction of the hand ipsilateral to the TMS stimulus was determined using correlation analysis.

3.2.8 Statistical analysis

All data were checked for normal distribution using the Shapiro-Wilk test. Log-transformation was used for variables that revealed not normal. The analyses were done on the transformed data using SPSS (version 22.0) but all variables are reported in their original, non-transformed, form as mean ± standard deviation.

Visuomotor performance, MEPs, SICI, ICF, IHI, and CLF pre- and post-intervention were compared by a three (Group) by two (Time) repeated measures analysis of variance (ANOVA) on Time for each side (Left, Right) separately. In case of a significant F-value for the Group by Time interaction effect, Tukey's post-hoc calculations for repeated measures ANOVA were performed to identify means that differed at $p < 0.05$. A Greenhouse-Geisser correction was used when the assumption of sphericity was violated. Pearson correlation analysis was used to identify significant relationships between behavioral and neurophysiological variables at $p < 0.05$.

3.3 RESULTS

3.3.1 Behavioral data

Figure 3.2 shows the Group by Time interaction ($F_{2,22} = 9.7$, $p = 0.001$) in motor learning. All three groups improved motor performance but the decrease in error was greater ($p < 0.05$) in MP (7.7°) and MP+SES (6.7°) compared with SES (2.9°). Figure 3.2 also shows that the magnitude of transfer of the learned skill after a right-hand visuomotor

intervention to the non-intervention left hand was similar: 4.4° (MP), 3.0° (SES), and 3.2° (MP+SES) (Time main effect, $F_{2,22} = 110.1$, $p < 0.001$). The control group showed 2.1° (10%) and 2.5° (10%) less error in the intervention and non-intervention hand respectively. In the remainder of the paper, we report the learning and transfer data adjusted for the effects of familiarization by subtracting the familiarization effects from the effects produced by the interventions. Tables 3.1 and 3.2 summarize the absolute and percent changes in motor learning.

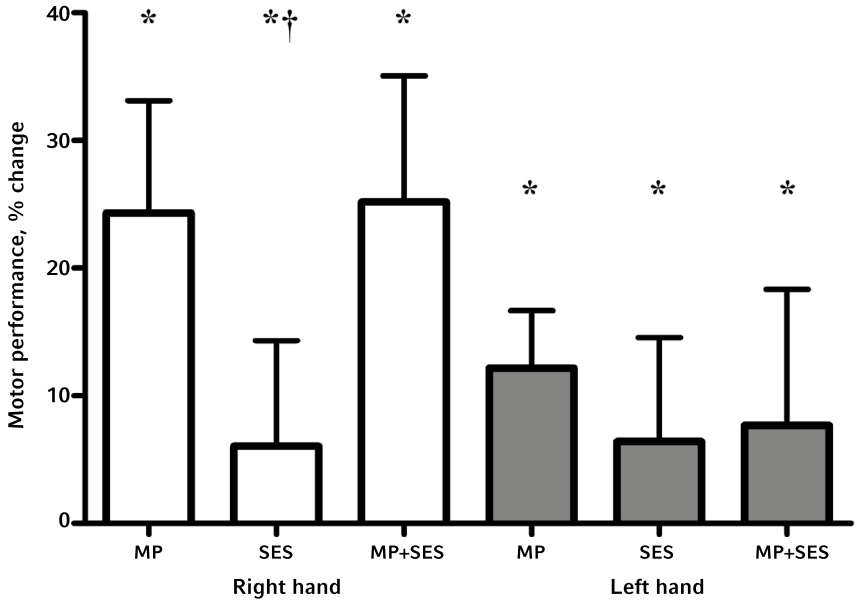

Figure 3.2. *Increases in motor performance after motor practice (MP), somatosensory electrical stimulation (SES), and MP+SES in the intervention (open bars) and non-intervention (filled bars). Motor performance was computed as a reduction in template-matching errors. Performance improved more after MP and MP+SES in the right hand compared to SES. *, significant Time main effect ($p < 0.05$, open and filled bars, respectively pooled, not graphed); †, significant Group by Time interaction ($p < 0.05$). Vertical bars denote +1SD.*

3.3.2 Corticospinal excitability data

Figure 3.3 shows MEPs in the left M1 (Figure 3.3A, 3B, 3C) and right M1 (Figure 3.3D, 3E, 3F) in a representative participant in each group. Figure 3.4A shows the Group by Time interaction in the Mmax-normalized MEPs: the 44% and 63% increase in MP and SES, respectively, were greater than the 19% increase in MP+SES (Group by Time interaction, $F_{2,19} = 3.9$, $p = 0.039$). Figure 3.4B shows that changes in MEPs in the non-intervention right M1 were higher in SES (54%) compared with MP (1%) and MP+SES (-14%) (Group by Time interaction, $F_{2,20} = 4.6$, $p = 0.023$). None of the interventions modulated the magnitude of the Mmax in the intervention right hand (MP: 3.8 to 4.0 mV; SES: 2.8 to 3.0 mV; MP+SES: 4.7 to 4.6 mV; all $p > 0.05$) and the non-intervention left hand (MP: 4.3 to 4.2 mV; SES: 3.1 to 3.2 mV; MP+SES: 3.6 to 3.7 mV; all $p > 0.05$). Tables 3.2 and 3.3 summarize the relative and absolute changes in corticospinal excitability.

Table 3.1: Intervention effects on motor learning in the intervention right and non-intervention left hand

		Pre Mean (± SD)	Post Mean (± SD)
Right			
	MP	19.6 (2.2)	11.8 (1.5)
	SES	17.8 (1.9)	14.9 (1.8)
	MP+SES	18.2 (3.9)	11.5 (1.4)
	Control	22.5 (1.8)	20.4 (4.1)
Left			
	MP	19.8 (1.8)	15.4 (1.3)
	SES	17.7 (2.7)	14.7 (1.4)
	MP+SES	17.0 (2.5)	13.8 (1.4)
	Control	25.0 (0.6)	22.4 (1.9)

Values are in degrees, expressing the mean absolute error from the target. MP: motor practice; SES: somatosensory electrical stimulation; MP+SES: motor practice combined with somatosensory electrical stimulation.

Table 3.2: Summary of percent changes in motor learning and TMS metrics in the right intervention and left non-intervention M1.

Right hand or left M1	MP	SES	MP+SES
Motor learning †	29.3*	6.1*	25.2*
CSE †	43.6*	63.4*	18.9*
SICI	16.4	21.3	1.6
ICF	21.4	14.7	1.5
IHI †	14.2*	-7.9*	-1.1
CLF †	34.1*	-14.1*	1.1
Left hand or right M1			
Motor learning	12.2*	6.4*	7.7*
CSE †	1.3	54.2*	-13.7
SICI †	6.1	-21.8*	41.4*
ICF	21	-3.4	-2.2
IHI	-9.5	-6.5	-1.8
CLF	3	-0.2	-14.8

*Values are mean percent changes based on individually computed changes. MP: motor practice; SES: somatosensory electrical stimulation; CSE: corticospinal excitability; SICI: short-interval intracortical inhibition (positive change denote decreases in inhibition); ICF: intracortical facilitation; IHI: interhemispheric inhibition (positive change denote reductions in inhibition); CLF: contralateral facilitation. * $p < 0.05$ based on Tukey's post-hoc test; † group by time interaction.*

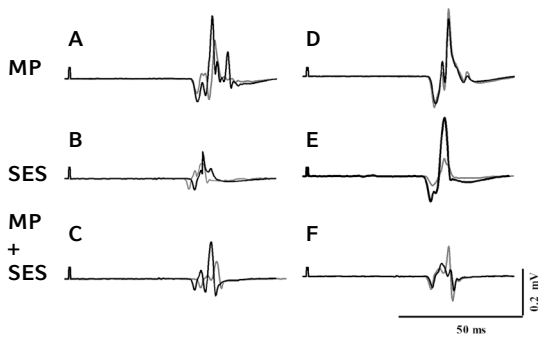

Figure 3.3. *Raw data of changes in corticospinal excitability after motor practice (MP) and somatosensory electrical stimulation (SES). Representative 10-trial-averaged motor evoked potentials (MEPs) measured in the extensor carpi radialis (ECR) representing changes in corticospinal excitability before (grey lines) and after (black lines) the three interventions in the intervention left M1 (A, B, C) and non-intervention right M1 (D, E, F).*

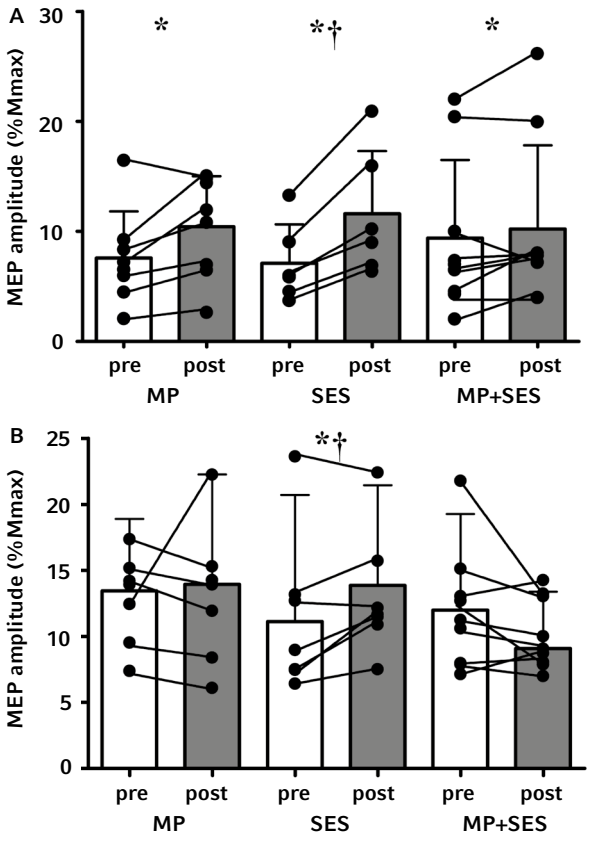

Figure 3.4. *Corticospinal excitability increases in all groups in the intervention M1 and after somatosensory electrical stimulation (SES) in the non-intervention M1. Corticospinal excitability before (open bars) and after (filled bars) the three interventions in the intervention left M1 (Panel A) and non-intervention right M1 (Panel B). Corticospinal excitability increased more after SES compared to MP and MP+SES in both M1s Interconnected dots represent individual changes and vertical bars denote +1SD. *, significant Time main effect ($p < 0.05$); †, significant Group by Time interaction ($p < 0.05$).*

3.3.3 Intracortical excitability data

The interventions did not modify SICI (Group by Time interaction, $F_{2,21} = 0.6$, $p = 0.565$) in the intervention left M1. Figure 3.5 shows that the three interventions modified SICI differently in the non-intervention right M1 (Group by Time interaction, $F_{2,21} = 4.2$, $p = 0.028$): the 41% decrease in inhibition after MP+SES (41%) was greater ($p < 0.05$) than the 6% and -22% in MP and SES, respectively, with these two latter values also different from one another ($p < 0.05$). There were no changes in ICF in either hemisphere. Tables 3.2 and 3.3 summarize the relative and absolute changes in intracortical excitability.

3.3.4 Interhemispheric excitability data

Figure 3.6A shows that the 8% longer iSP duration, reflecting higher IHI after MP was greater than the -1% change after MP+SES and the -14% shortening of iSP after SES (Group by Time interaction, $F_{2,20} = 3.7$, $p = 0.044$). In contrast, iSP duration remained unchanged in the non-intervention right M1 ($F_{2,18} = 0.2$, $p = 0.789$).

During contraction of the left ECR there is some associated activity in the 'resting' right ECR. We quantified if the interventions modified the magnitude of this associated activity and also the facilitation of MEPs produced by TMS. Figure 3.6B shows that the three interventions modified this facilitation differently (Group by Time interaction, $F_{2,21} = 3.6$, $p = 0.044$): facilitation was similar after MP (14%) and MP+SES (1%) but greater than after SES (-8%). Also, the unchanged facilitation after MP+SES (i.e., 1%) was different from the 8% decrease after SES. The interventions did not modify the MEP facilitation in the left ECR during right ECR contraction ($F_{2,21} = 1.0$, $p = 0.379$). Table 3.2 and 3.4 summarize percent and absolute changes in interhemispheric data.

Table 3.3: Effects of three interventions on corticospinal and intracortical excitability

	Pre Mean (± SD)	Post Mean (± SD)
Right M1		
CSE		
MP	7.6 (4.2)	10.4 (4.6)
SES	7.1 (3.6)	11.6 (5.7)
MP+SES	9.4 (7.1)	10.2 (7.6)
SICI		
MP	28.6 (20.20)	70.9 (43.1)
SES	49.6 (14.2)	60.1 (21.3)
MP+SES	58.0 (33.5)	54.5 (31.7)
ICF		
MP	133.2 (50.6)	142.8 (31.6)
SES	165.1 (78.9)	164.6 (43.2)
MP+SES	145.1 (61.3)	136.2 (48.6)
Left M1		
CSE		
MP	13.4 (5.5)	13.9 (8.3)
SES	11.1 (9.6)	13.9 (7.6)
MP+SES	12.0 (7.3)	9.1 (4.3)
SICI		
MP	51.2 (25.8)	54.6 (33.0)
SES	58.5 (15.1)	45.5 (18.3)
MP+SES	58.5 (26.0)	73.8 (31.2)
ICF		
MP	133.5 (39.6)	158.7 (44.7)
SES	135.2 (19.5)	128.7 (17.1)
MP+SES	175.8 (99.0)	157.6 (69.1)

CSE: corticospinal excitability (% maximal compound action potential); SICI: short-interval-intracortical inhibition (% test pulse size); ICF: intracortical facilitation (% test pulse size). Figures 3.4A and 4B illustrate the significant interaction effects for corticospinal excitability in the left and right M1 respectively. Figure 3.5 denotes a significant interaction effect for SICI in the right M1.

3.3.5 Correlation analyses

Increases in visuomotor performance in the right and left hand did not correlate (r = 0.32, p = 0.119). Changes in right hand visuomotor performance did not correlate with increases in corticospinal excitability measured in the left M1 (r = -0.17, p = 0.210), nor were the changes in left hand visuomotor performance associated with changes in corticospinal excitability measured in the right M1 (r = -0.19, p = 0.189). However, increased facilitation of right ECR MEPs during left hand contraction (CLF) weakly correlated with increased visuomotor performance in the right hand (r = 0.45, p = 0.013). Changes in iSP did not correlate with increases in visuomotor performance. There was no correlation between the changes in corticospinal excitability in the left M1 and right M1 (r = 0.11, p = 0.310), but the increase in corticospinal excitability in the right M1 weakly correlated with the decrease in SICI in the right M1 (r = -0.37, p = 0.039). Also, there was a positive correlation between changes in iSP duration in the left ECR and facilitation of the MEPs in the left ECR during right ECR contractions (CLF; r = 0.49, p = 0.007). Changes in bEMG in the right ECR did not correlate with changes in facilitation of MEPs in the right ECR during left hand contractions (CLF; r = 0.26, p = 0.216).

3.4 DISCUSSION

We found that all three interventions produced motor learning and interlimb transfer but SES added to MP did not further increase learning and transfer (Table 3.2). Corticospinal excitability strongly increased after MP and SES when measured at rest but it increased after MP and decreased after SES when measured during contraction. No changes occurred in SICI and ICF in the intervention M1. MP did not affect any of the TMS metrics in the non-intervention transfer M1. In contrast, corticospinal excitability strongly increased and SICI strongly decreased in the non-intervention M1 after SES, while MP+SES showed the opposite of these effects. In the non-intervention M1, the increase in corticospi-

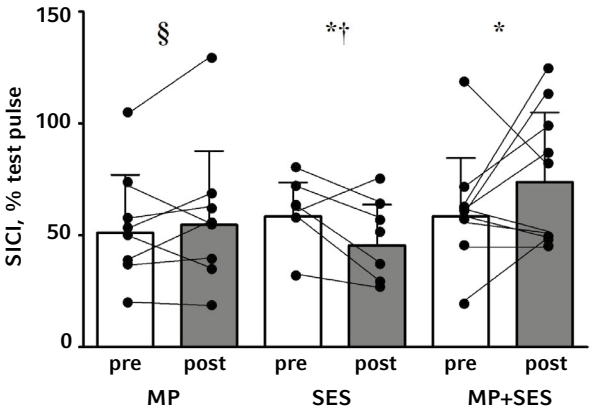

Figure 3.5. *Group and individual changes in short-interval intracortical inhibition (SICI) after motor practice (MP), somatosensory electrical stimulation (SES), and MP+SES in the non-intervention right M1. Conditioned motor evoked potentials (MEP) before (open bars) and after (filled bars) the three interventions. Lower values for SICI represent higher intracortical inhibition. Group data show that SICI increased after SES and decreased after MP+SES in the non-intervention M1 while MP did not modify SICI. Interconnected dots represent individual changes and vertical bars denote +1SD. *, significant Time main effect (p < 0.05); † and §, significant Group by Time interaction (p < 0.05).*

nal excitability correlated with decreases in intracortical inhibition. MP and SES affected interhemispheric excitability in the opposite direction. In total, the present study showed that MP and SES each can produce motor learning and interlimb transfer but these effects are non-additive and are likely mediated by different mechanisms.

3.4.1 Effects of motor practice on motor performance

3.4.1.1 Practice hand

Participants naïve to the task showed 27% learning in the intervention hand after 25 minutes of visuomotor practice (Figure 3.2). The 27% learning is comparable with the improvements in the ankle (23%) [27] and metacarpophalangeal joint of the index finger (23%) [32] after a similar paradigm and practice duration. The magnitude of learning in the practiced hand is roughly within the range of changes produced by other learning paradigms using a force-control tracking task (36%) [37]. The common element in these single-session learning regimes is that they all represent the rapid, initial phase of motor learning [38].

Table 3.4: Effects of three interventions on interhemispheric excitability

	Pre Mean (± SD)	Post Mean (± SD)
Left M1		
iSP		
MP	22.2 (3.4)	25.1 (3.7)
SES	27.5 (3.4)	25.2 (5.7)
MP+SES	28.1 (8.5)	27.6 (7.0)
CLF		
MP	169.0 (52.5)	222.5 (77.5)
SES	170.1 (74.3)	127.8 (43.5)
MP+SES	222.8 (141.4)	214.1 (113.9)
Right M1		
iSP		
MP	25.7 (4.8)	22.4 (4.0)
SES	24.7 (1.8)	24.1 (6.2)
MP+SES	27.2 (7.4)	24.9 (5.3)
CLF		
MP	198.5 (81.1)	204.6 (113.5)
SES	177.5 (78.8)	164.6 (41.3)
MP+SES	188.8 (68.7)	153.4 (34.8)

iSP: ipsilateral silent period (ms); CLF: contralateral facilitation (% MEP during contralateral hand contracting and MEP during contralateral hand resting). Figures 3.6A and 3.6B illustrate the significant interaction effects for ipsilateral silent period and contralateral facilitation in the let M1, respectively.

3.4.1.2 Interlimb transfer

Remarkably, practice with voluntary contractions as well as SES, which lacks a voluntary element, both produced interlimb transfer that was statistically similar (Figure 3.2, for a review see [39]). The average 9% net interlimb transfer in the present study was comparable with the 13% produced by a ball rotation task requiring complex finger movements [40] but both were much smaller than the 62% produced by 300 ballistic finger movements also completed in one session [41]. Theories of interlimb transfer imply that the magnitude of transfer is proportional to the magnitude of learning [39], a conjecture supported by the $r = 0.71$ ($p < 0.001$) correlation between increases in force of the trained and untrained hand in chronic cross-education studies using low-skill, high force unilateral muscle contractions ([42], personal communication). However, this association tends to be lower after rapid tapping movements ($r = 0.44$, $p = 0.04$; [41]) or can be absent when the skill is complex as were the case after a ball rotation task ($r = -0.07$, $p = 0.86$; [40], personal communication). The low or altogether absent associations may become stronger after additional practice that consolidates the motor skill into memory [43]. Alternatively, participants may rely on procedural elements when they perform the task with the non-practice hand, resulting in 'transfer'. We did notice

that learning in the intervention (r = 0.53, p = 0.006) and in the transfer hand (r = 0.59, p = 0.002) was associated with the skill level at baseline, suggesting that, if used in a clinical setting, patients with low motor function would benefit most from this type of motor practice. Collectively, the behavioral data are in line with existing evidence suggesting that visuomotor skill practice is an effective and reliable model of motor learning, a model that is now extended to the wrist joint.

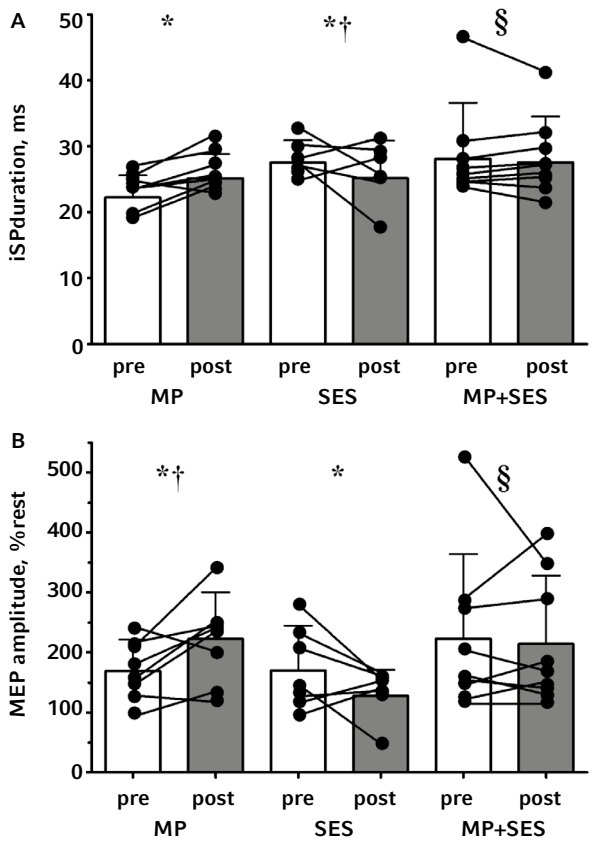

Figure 3.6. *Group and individual changes in interhemispheric inhibition (IHI) and facilitation (CLF) after motor practice (MP) and somatosensory electrical stimulation (SES). IHI and CLF from the left M1 to the right M1 graphed before (open bars) and after (filled bars) the three interventions. IHI decreased after SES but increased after MP, resulting in a cancelation effect after MP+SES (Panel A). Opposite effects were found for CLF (Panel B). Interconnected dots represent individual changes and vertical bars denote +1SD. *, significant Time main effect (p < 0.05); † and §, significant Group by Time interaction (p < 0.05).*

3.4.2 Effects of SES on motor performance

3.4.2.1 Direct and crossed effects of SES

We found some evidence that SES on its own can increase healthy adults' skill performance by 6% (Figure 3.2 and Table 3.1; p = 0.002). Our results are in line with the broad concept that sensory inputs are powerful modulators of motor performance when administered in the form of SES [9], mirror visual feedback [40], auditory cueing [44], and muscle warming [45]. In addition to the direct effects, SES also produced non-focal, crossed effects because the non-intervention hand's skill performance also improved (6%, p = 0.001). Neuroanatomical, electrophysiological, and imaging data revealed that unilateral electrical stimulation, including SES, can activate the contralateral S1 and S2

bilaterally [11,13,14,46-48]. Direct connections between Brodmann areas 1 and 2 of S1 and M1 [49-52], and S2 and M1 [51] provide a neuroanatomical basis for the observed effects. The mechanism of how monotonic, non-patterned SES pulses improve complex skills is unclear. Electrical stimulation, however, can facilitate motor learning and skill retention by entraining sensorimotor rhythms [53] and by having selective effects on oscillatory frequencies underlying motor learning [54]. Taken together, the current data provide for the first time evidence that weak electrical nerve stimulation in the form of SES can produce small but statistically and functionally meaningful interlimb transfer in healthy adults.

3.4.2.2 Direct and crossed effects of MP+SES

We also tested if SES combined with MP had an additive effect on skill learning compared with MP or SES. Although MP alone and SES alone increased motor learning by 29% and 6%, respectively, SES combined with MP did not further increase learning (25%; Table 3.2). We expected to find an additive effect because SES activated S1-M1 projections in animal and human brains [11,12,19,55] and caused M1 reorganization in rats [56] and healthy humans [14,19]. In addition, combining MP with SES is an effective method to alter sensory states in spinal cord injury patients suffering from sensory deficits [57,58]. Notwithstanding these data, we found no additive effect, suggesting that MP might have saturated the circuits SES also accessed, the overlap between the circuits activated by MP and SES was functionally inefficient, or the effects produced by MP and SES interfered with each other. A lack of an additive effect was perhaps also due to the effect of SES alone being small (6%) in proportion to the 29% learning produced by MP so that SES could not manifest itself when SES was added to motor practice. An additive effect may still be possible after future studies determine the SES parameters that produce the greatest learning effects.

We also examined the effects of SES combined with MP on interlimb transfer. Our expectation for SES augmenting interlimb transfer was based partly on neuroanatomical paths implicated in such a transfer and on data showing that afferent inputs, in the form of mirror-viewing the hand performing while motor practice, however different from SES, produced 13% greater skill transfer to the resting hand [40]. Despite the plausibility of this hypothesis, we found no evidence for SES augmenting the transfer of a visuomotor skill. Perhaps the level of activation of somatosensory areas ipsilateral to the stimulation by SES was less than reported in previous studies (for a review see [29]), making SES ineffective. It is also possible that MP+SES did not cause additional learning as a result of an interference effect, reflected by opposite adaptations in TMS metrics discussed in following sections. Although the methodological elements in the current study were based on previous studies [29], we demonstrated no additive effect of SES on motor skill learning in the practiced and the non-practiced hand in healthy young adults.

3.4.3 MP and SES modify corticospinal excitability

3.4.3.1 Direct effects of MP

In agreement with the hypothesis and the prevailing literature, 300 voluntary movements forming 25 minutes of visuomotor practice increased corticospinal excitability by ~40%

measured at rest (Figure 3.4A, [27,28,32]). Increases in MEP size after short-term motor practice are thus common and presumably reflect use-dependent plasticity [59,60] through long-term potentiation-like mechanisms in motor cortical circuits [43,61,62]. Although it has been reported that M1 is involved in motor learning and early consolidation of motor memories (e.g. [43]), increases in corticospinal excitability in the intervention left M1 did not correlate with the behavioral changes in the intervention right hand ($r = -0.17$, $p = 0.210$, $n = 24$), as was also the case in a previous study [32]. A lack of correlation between corticospinal excitability and behavioral changes complements the findings of an earlier study in which 5 Hz repetitive TMS over the M1 reduced corticospinal excitability but did not interfere with motor learning [63]. We speculate that two factors complicate the interpretation of the present and past results and underlie the lack of correlation. One factor is that changes in corticospinal excitability measured at rest may reflect the altered state of circuits that are different from the ones that become active during the learning task. Measurements of corticospinal excitability during the task or muscle contraction may be a more relevant outcome than corticospinal excitability measured at rest. Second, there is a temporal asynchrony between the changes in corticospinal excitability so that the peak changes in each variable occur at different times. Finally, it is also possible that the neurophysiological measures as performed with TMS do not directly reflect changes in excitability essential for motor learning in this context. Despite such caveats the results of the present and past studies seem all to confirm the putative role of M1 in motor learning.

3.4.3.2 Crossed effects of MP

In contrast to the changes seen in the left-intervention M1, corticospinal excitability remained unchanged in the non-intervention right M1 after MP despite evidence for 10% learning (Figure 3.4B) and previous studies reporting increased corticospinal excitability in the non-intervention M1 after ballistic motor practice [41,64]. Increases in corticospinal excitability may be task-dependent because MEP amplitude in the non-intervention M1 also did not change after a sequence learning task [65]. Repetitive recruitment of the same corticospinal paths in ballistic motor practice in contrast with tasks involving multiple muscles may explain the differential effects on corticospinal excitability after ballistic motor practice [66]. Corticospinal excitability may not be an optimal neurophysiological marker for motor learning because MP produced transfer without changes in corticospinal excitability, suggesting that structures and/or cortical circuits other than corticospinal paths originating from the M1 ipsilateral to the practicing hand may play a more prominent role in interlimb transfer.

3.4.3.3 Direct and crossed effects of SES

Unlike MP, SES strongly increased corticospinal excitability in both M1s (Figure 3.4A and 3.4B, Table 3.3). Increases in corticospinal excitability after SES has been shown in a range of muscles and body parts [23,67,68]. The magnitude of change in the stimulated hand in the present study was 63.4% (Table 3.3), fitting within the range of the 50% to 96% increases reported previously [29]. Our data provide a hint that the SES-adaptations may be non-linear with respect to the duration of the stimulation because we observed a 63% increase after only 25 minutes of SES in the ECR, a change crudely similar to 77% reported after 120 minutes of SES in the first dorsal interosseous muscle [20,23,25,69] and

abductor digiti minimi muscle [20]. A plateau of 50% increase in corticospinal excitability reached after 45 minutes of SES fits in this non-linear dose-response relationship [22]. In the non-intervention right M1, corticospinal excitability increased 54.2%, considerably more than the 9.4% increase after a paired associative stimulation paradigm delivered at 0.25 Hz for 15 minutes [26]. Taken together, the present study replicated previous findings showing that SES can increase corticospinal excitability in the SES-stimulated M1 in humans and provide new evidence that SES to a peripheral nerve only increases corticospinal excitability non-focally in the non-intervention M1 considerably.

3.4.3.4 Direct and crossed effects of MP+SES

Against expectations, SES combined with MP did not have an additive effect on corticospinal excitability in the intervention M1. Instead, SES seemed to interfere with MP because MP (43.6%) and SES (63.4%) increased corticospinal excitability substantially more than SES combined with MP (18.9%; Table 3.3). SES added to chronic massed motor practice in spinal cord injury patients also did not additionally increase corticospinal excitability [57]. Possibly, the combined input is too high for motor cortical neurons to process MP and SES concurrently. MP saturates the corticospinal circuits and leaves no room for SES to additionally increase corticospinal excitability. In the non-stimulated right M1, SES also had no additive effect on corticospinal excitability rather corticospinal excitability actually decreased by 13.7%. Still, to exploit any potential effects of SES on motor learning, future studies could explore if SES applied as sensory priming before MP could potentiate learning. In sum, combining MP with SES did not have an additive effect on corticospinal excitability in either M1 in healthy young participants probably due to a saturation effect.

3.4.4 Intracortical excitability

3.4.4.1 Direct effects on SICI

Motor learning [27,32,70-72] and SES [20] tend to decrease SICI in healthy young adults and patients (range: 7 to 80%). Reductions in $GABA_A$-mediated SICI involve long-term-potentiation like processes [61] in inhibitory horizontal connections [73]. Visuomotor training in the first dorsal interosseous and ankle muscles reduced SICI 38% [32] and 50% [27], respectively. In the present study however, we observed a non-significant 13.1% reduction in SICI in the left intervention-M1 after MP, SES, and MP+SES (time main effect, $F = 0.133$, $p = 0.719$) and no relationship between the changes in SICI and motor learning ($r = -0.22$, $p = 0.297$) in agreement with previous findings [32,71]. There was large variation in the SICI responses among the participants: 12, 3, and 9 of the 24 participants, respectively, showed decreases, no change, or increases. We were also unable to discern sub-groups of responders and non-responders to MP or SES in terms of SICI [74]. Because involvement of long-term-potentiation-like processes has been suggested to modify M1 metrics in response to both visuomotor training and SES, perhaps these interventions act on similar brain areas (e.g., premotor cortex) and one would expect a positive interaction between the two types of interventions with respect to SICI. However, our data show an opposite effect of MP and SES on SICI (Figure 3.5). The changes in SICI are possibly related to changes in corticospinal excitability in the non-intervention M1, although absence of correlations complicate these speculations.

Similarly to SICI, NMDA-mediated intracortical facilitation, ICF, did not change after motor practice and SES in line with some [20,27] but not with other studies [7]. In sum, it appears that SICI and ICF-related mechanisms are marginally involved in visuomotor and SES-related adaptations under the present experimental conditions. Because the methodological details of collecting the SICI, ICF, and visuomotor data were similar in the present and previous studies, the discrepancies between studies remain unclear.

3.4.4.2 Crossed effects on SICI

Recently there has been a heightened interest in the role and function of the M1 ipsilateral to motor practice and sensory input [29,75]. In a larger perspective, these studies revealed that iM1 plasticity to short and long term motor and sensory interventions is a part of the adaptive network that can contribute to improved motor function as in aging [76]. In agreement with previous studies [65,77], we observed reductions in SICI in the non-intervention right-ipsilateral M1 after MP (6%) and MP+SES (41%) that were different from increases in SICI after SES-only intervention (-22%; Figure 3.5; interaction, $p = 0.028$). Past and current findings suggest that inhibition within the hemisphere receiving the transfer may be involved in the transfer of motor output. One mechanism could act through corticospinal excitability because the increase in corticospinal excitability correlated weakly but significantly with reductions in SICI in the non-intervention M1 ($r = -0.37$, $p = 0.039$). However, we found no relationship between changes in SICI in the non-intervention right-ipsilateral M1 and increases in motor performance in the non-intervention left hand ($r = -0.11$, $p = 0.599$), making a definitive interpretation at best speculative. In contrast with the decreased ipsilateral SICI after interventions including MP, the unique effect of SES alone on ipsilateral SICI requires special attention because we observed a non-significant 22% ($p = 0.144$) increase instead of an expected decrease in the non-intervention M1 after SES. Based on neuroanatomical connections described earlier, the expectation is that SES-generated afferent volleys would decrease the excitability of horizontal inhibitory connections resulting in a decrease instead of an increase in SICI after SES. Our results are somewhat paradoxical because we observed a 54.2% increase in corticospinal excitability, known to be associated with SICI, after SES. Facilitation of GABAA receptors, involved in SICI [78], interferes with intervention-induced increases in corticospinal excitability [61]. Considering the boundaries of the present study we are not able to resolve this unexpected finding but one possibility is that factors other than SICI are also involved in increases in corticospinal excitability in the non-intervention M1 after SES (e.g., IHI as discussed in the next section). In contrast with SICI, ICF was not modified in both the intervention and non-intervention M1 consistent with earlier studies after motor practice [77,79] and SES [20], suggesting inhibitory compared with excitatory interneurons are more sensitive to MP and SES. Taken together, ipsilateral MP and SES modified SICI differently, and the current data provide a hint that SES added to MP additionally decreases the inhibition in the ipsilateral M1 after MP. However, future studies are needed to confirm this effect and in addition examine other forms of inhibition and correlate the changes in behavior and the M1 metrics in an effort to better understand the nature of involvement of the ipsilateral M1 in motor learning.

3.4.5 Interhemispheric inhibition and facilitation

During a unilateral motor task, IHI suppresses undesired activity in the 'inactive' hemisphere and in a bimanual task, IHI is also related to the coordination of motor activity [80]. Increased use of one hand can lead to interlimb transfer that concomitantly modifies IHI measured at rest and measured during a muscle contraction. For example, 1,000 submaximal voluntary contractions of the right-dominant FDI produced 28% transfer of voluntary force to the FDI of the non-dominant left hand with a 31% concomitant decrease in IHI at rest and these reductions progressively became more strongly associated with interlimb transfer [81]. This association between IHI and motor performance was also shown after only a 30-minute serial reaction-time task intervention [65]. However, data are inconsistent because a decrease in IHI was not associated with interlimb transfer of a finger tapping sequence [77] and IHI did not change after a complex ball rotation task [40]. In the present study, we used the iSP to quantify changes in IHI [65,82,83] and observed bidirectional effects: MP increased and SES decreased IHI, respectively, by 14.2% and 7.9% (both $p < 0.001$; Table 3.4, Figure 3.6A) and MP+SES had no effect on IHI (1.2% change). Similar but opposite effects were also seen for another measure of interhemispheric excitability, MEPs conditioned by a contralateral muscle contraction (contralateral facilitation, Figure 3.6B). The 14.2% increase in IHI as measured by iSP is inconsistent with some data [65] but agrees with other data [84]. An increase in IHI after MP would favour the interpretation that MP with one hand modifies the excitability of interhemispheric connections in order to preserve or even increase motor independence of the two hands. The 7.9% decrease in IHI as measured by iSP after SES suggests that sensory input can modify the state of the non-intervention M1. Near motor threshold SES produces afferent volleys that reach S1 and bilaterally S2 [11,14-16]. Consistent with previous suggestions, such inputs can modify the excitability state of the iM1 through iS2-iM1 and M1-M1 connections, giving rise to reduced IHI from stimulated to non-stimulated M1 [26]. In view of the individual negative and positive effects of MP and SES on IHI, the unchanged IHI after MP+SES suggests the presence of a cancelation or interference effect. The neuroanatomical basis of such effects are not entirely clear because crossed effects of MP and SES are transferred trough callosal fibers in the central part of the corpus callosum [85] and bilateral S2 activation, respectively. Inhibitory inputs to iM1 from M1 and excitatory input from iS1 and iS2 to iM1 could sum to a net cancelation effect. We are currently examining the possibility that giving SES before instead of during MP could potentiate motor learning by priming the paths involved in IHI. Taken together, the MP and SES each can uniquely modify ipsilateral motor function in healthy young adults, with the combined effects resulting in a cancelation.

3.4.6 Clinical perspective

Surprisingly, studies using SES so far have almost exclusively focussed on stroke patients, showing some promise as an adjuvant to rehabilitation of impaired motor function [6-8,10]. However, only one of these clinical trials included an age- and gender matched healthy control group. The present study expands the clinical data by showing that SES alone or in combination with MP has specific direct and crossed effects on motor performance and neuronal excitability in healthy young adults. Although the present study did not show additive effects of SES if combined with MP in healthy adults, such an effect may be present in patients, because SES effects seem to depend on participants'

clinical status: the effects are much less (6%) in healthy compared to stroke participants 27% [8]. An increased understanding of the mechanisms including cortical, subcortical, and spinal involvement underlying these effects will likely contribute to an optimal protocol for the rehabilitation of patients suffering from unilateral neurological and orthopaedic disorders.

3.4.7 Limitations and conclusion

One limitation of the present study was that SES stimulation parameters were not systematically varied [86,87]. It is possible that optimal SES parameters differ between healthy participants and patients. Second, we, as many previous studies, performed the majority of the excitability measurements at rest yet the intervention involved motor activity. Therefore, the excitability results could be different when assessed not at rest but during muscle contraction. Third, we did not perform measures of spinal excitability. Although SES does not modify F-wave characteristics [23], we cannot completely rule out the possibility that changes in spinal excitability might have contributed to the observed effects. For example, ascending sensory and descending motor information integrate in common spinal interneurons [88], possibly contributing to this involvement. Next, this study involved small groups of participants and some of the measurements revealed large variation, complicating interpretation. Finally, we did not control for environmental factors, so it is possible that changes in excitability measures are caused by experimental factors such as locus of attention or visual feedback [89].

In conclusion, MP-induced learning is most likely mediated by increased corticospinal drive at rest and during contraction. SES-induced learning is most likely the result of an upregulation of corticospinal excitability at rest possibly mediated by decreased inhibition. The physiological mechanism of transfer produced by MP remains elusive under these conditions, whereas the SES-induced transfer involves increased corticospinal excitability most likely linked to the bilateral S2 activation and its action on the M1 ipsilateral to the SES-stimulated hand. These conclusions are complicated by an absence of relevant correlations between behavioral and neuronal changes. In total, the present study showed that MP and SES each can produce motor learning and interlimb transfer but these effects are non-additive and are likely mediated by different mechanisms.

REFERENCES

1. Rosenkranz K, Rothwell JC. Modulation of proprioceptive integration in the motor cortex shapes human motor learning. J Neurosci. 2012;32: 9000-9006.

2. Gentilucci M, Toni I, Daprati E, Gangitano M. Tactile input of the hand and the control of reaching to grasp movements. Exp Brain Res. 1997;114: 130-137.

3. Rothwell JC, Traub MM, Day BL, Obeso JA, Thomas PK, Marsden CD. Manual motor performance in a deafferented man. Brain. 1982;105 (Pt 3): 515-542.

4. Nudo RJ, Friel KM, Delia SW. Role of sensory deficits in motor impairments after injury to primary motor cortex. Neuropharmacology. 2000;39: 733-742.

5. Sawaki L, Wu CW, Kaelin-Lang A, Cohen LG. Effects of somatosensory stimulation on use-dependent plasticity in chronic stroke. Stroke. 2006;37: 246-247.

6. Conforto AB, Cohen LG, dos Santos RL, Scaff M, Marie SK. Effects of somatosensory stimulation on motor function in chronic cortico-subcortical strokes. J Neurol. 2007;254: 333-339.

7. Celnik P, Hummel F, Harris-Love M, Wolk R, Cohen LG. Somatosensory stimulation enhances the effects of training functional hand tasks in patients with chronic stroke. Arch Phys Med Rehabil. 2007;88: 1369-1376.

8. Koesler IB, Dafotakis M, Ameli M, Fink GR, Nowak DA. Electrical somatosensory stimulation improves movement kinematics of the affected hand following stroke. J Neurol Neurosurg Psychiatry. 2009;80: 614-619.

9. Sorinola IO, Bateman RW, Mamy K. Effect of somatosensory stimulation of two and three nerves on upper limb function in healthy individuals. Physiother Res Int. 2012;17: 74-79.

10. Wu CW, Seo HJ, Cohen LG. Influence of electric somatosensory stimulation on paretic-hand function in chronic stroke. Arch Phys Med Rehabil. 2006;87: 351-357.

11. Allison T, McCarthy G, Wood CC, Williamson PD, Spencer DD. Human cortical potentials evoked by stimulation of the median nerve. II. Cytoarchitectonic areas generating long-latency activity. J Neurophysiol. 1989;62: 711-722.

12. Allison T, McCarthy G, Wood CC, Jones SJ. Potentials evoked in human and monkey cerebral cortex by stimulation of the median nerve. A review of scalp and intracranial recordings. Brain. 1991;114 (Pt 6): 2465-2503.

13. Forss N, Hari R, Salmelin R, Ahonen A, Hamalainen M, Kajola M, et al. Activation of the human posterior parietal cortex by median nerve stimulation. Exp Brain Res. 1994;99: 309-315.

14. Golaszewski SM, Siedentopf CM, Koppelstaetter F, Rhomberg P, Guendisch GM, Schlager A, et al. Modulatory effects on human sensorimotor cortex by whole-hand afferent electrical stimulation. Neurology. 2004;62: 2262-2269.

15. Hari R, Reinikainen K, Kaukoranta E, Hamalainen M, Ilmoniemi R, Penttinen A, et al. Somatosensory evoked cerebral magnetic fields from SI and SII in man. Electroencephalogr Clin Neurophysiol. 1984;57: 254-263.

16. Hari R, Hamalainen H, Hamalainen M, Kekoni J, Sams M, Tiihonen J. Separate finger representations at the human second somatosensory cortex. Neuroscience. 1990;37: 245-249.

17. Manto M, Oulad ben Taib N, Luft AR. Modulation of excitability as an early change leading to structural adaptation in the motor cortex. J Neurosci Res. 2006;83: 177-180.

18. Rosen I, Asanuma H. Peripheral afferent inputs to the forelimb area of the monkey motor cortex: input-output relations. Exp Brain Res. 1972;14: 257-273.

19. Wu CW, van Gelderen P, Hanakawa T, Yaseen Z, Cohen LG. Enduring representational plasticity after somatosensory stimulation. Neuroimage. 2005;27: 872-884.

20. Kaelin-Lang A, Luft AR, Sawaki L, Burstein AH, Sohn YH, Cohen LG. Modulation of human corticomotor excitability by somatosensory input. J Physiol (Lond). 2002;540: 623-633.

21. Ridding MC, McKay DR, Thompson PD, Miles TS. Changes in corticomotor representations induced by prolonged peripheral nerve stimulation in humans. Clin Neurophysiol. 2001;112: 1461-1469.

22. McKay D, Brooker R, Giacomin P, Ridding M, Miles T. Time course of induction of increased human motor cortex excitability by nerve stimulation. Neuroreport. 2002;13: 1271-1273.

23. Ridding MC, Brouwer B, Miles TS, Pitcher JB, Thompson PD. Changes in muscle responses to stimulation of the motor cortex induced by peripheral nerve stimulation in human subjects. Experimental brain research.Experimentelle Hirnforschung.Experimentation cerebrale. 2000;131: 135-143.

24. Mang CS, Clair JM, Collins DF. Neuromuscular electrical stimulation has a global effect on corticospinal excitability for leg muscles and a focused effect for hand muscles. Exp Brain Res. 2011;209: 355-363.

25. Charlton CS, Ridding MC, Thompson PD, Miles TS. Prolonged peripheral nerve stimulation induces persistent changes in excitability of human motor cortex. J Neurol Sci. 2003;208: 79-85.

26. Shin HW, Sohn YH. Interhemispheric transfer of paired associative stimulation-induced plasticity in the human motor cortex. Neuroreport. 2011;22: 166-170.

27. Perez MA, Lungholt BK, Nyborg K, Nielsen JB. Motor skill training induces changes in the excitability of the leg cortical area in healthy humans. Exp Brain Res. 2004;159: 197-205.

28. Jensen JL, Marstrand PC, Nielsen JB. Motor skill training and strength training are associated with different plastic changes in the central nervous system. J Appl Physiol (1985). 2005;99: 1558-1568.

29. Veldman MP, Maffiuletti NA, Hallett M, Zijdewind I, Hortobagyi T. Direct and crossed effects of somatosensory stimulation on neuronal excitability and motor performance in humans. Neurosci Biobehav Rev. 2014;47: 22-35.

30. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 1971;9: 97-113.

31. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 2009;120: 2008-2039.

32. Cirillo J, Todd G, Semmler JG. Corticomotor excitability and plasticity following complex visuomotor training in young and old adults. Eur J Neurosci. 2011;34: 1847-1856.

33. Panizza M, Nilsson J, Roth BJ, Basser PJ, Hallett M. Relevance of stimulus duration for activation of motor and sensory fibers: implications for the study of H-reflexes and magnetic stimulation. Electroencephalogr Clin Neurophysiol. 1992;85: 22-29.

34. Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, et al. Corticocortical inhibition in human motor cortex. J Physiol. 1993;471: 501-519.

35. Garry MI, Thomson RH. The effect of test TMS intensity on short-interval intracortical inhibition in different excitability states. Exp Brain Res. 2009;193: 267-274.

36. Solnik S, Rider P, Steinweg K, DeVita P, Hortobagyi T. Teager-Kaiser energy operator signal conditioning improves EMG onset detection. Eur J Appl Physiol. 2010;110: 489-498.

37. Floyer-Lea A, Matthews PM. Distinguishable brain activation networks for short- and long-term motor skill learning. J Neurophysiol. 2005;94: 512-518.

38. Dayan E, Cohen LG. Neuroplasticity subserving motor skill learning. Neuron. 2011;72: 443-454.

39. Ruddy KL, Carson RG. Neural pathways mediating cross education of motor function. Front Hum Neurosci. 2013;7: 397.

40. Nojima I, Mima T, Koganemaru S, Thabit MN, Fukuyama H, Kawamata T. Human motor plasticity induced by mirror visual feedback. J Neurosci. 2012;32: 1293-1300.

41. Lee M, Hinder MR, Gandevia SC, Carroll TJ. The ipsilateral motor cortex contributes to cross-limb transfer of performance gains after ballistic motor practice. J Physiol. 2010;588: 201-212.

42. Zhou S. Chronic neural adaptations to unilateral exercise: mechanisms of cross education. Exerc Sport Sci Rev. 2000;28: 177-184.

43. Muellbacher W, Ziemann U, Wissel J, Dang N, Kofler M, Facchini S, et al. Early consolidation in human primary motor cortex. Nature. 2002;415: 640-644.

44. Brown RM, Palmer C. Auditory and motor imagery modulate learning in music performance. Front Hum Neurosci. 2013;7: 320.

45. Immink MA, Wright DL, Barnes WS. Temperature dependency in motor skill learning. J Mot Behav. 2012;44: 105-113.

46. Blickenstorfer A, Kleiser R, Keller T, Keisker B, Meyer M, Riener R, et al. Cortical and subcortical correlates of functional electrical stimulation of wrist extensor and flexor muscles revealed by fMRI. Hum Brain Mapp. 2009;30: 963-975.

47. Deuchert M, Ruben J, Schwiemann J, Meyer R, Thees S, Krause T, et al. Event-related fMRI of the somatosensory system using electrical finger stimulation. Neuroreport. 2002;13: 365-369.

48. Iftime-Nielsen SD, Christensen MS, Vingborg RJ, Sinkjaer T, Roepstorff A, Grey MJ. Interaction of electrical stimulation and voluntary hand movement in SII and the cerebellum during simulated therapeutic functional electrical stimulation in healthy adults. Hum Brain Mapp. 2012;33: 40-49.

49. Donoghue JP, Sanes JN. Motor areas of the cerebral cortex. J Clin Neurophysiol. 1994;11: 382-396.

50. Friedman DP, Jones EG. Thalamic input to areas 3a and 2 in monkeys. J Neurophysiol. 1981;45: 59-85.

51. Jones EG. The nature of the afferent pathways conveying short-latency inputs to primate motor cortex. Adv Neurol. 1983;39: 263-285.

52. Kaneko T, Caria MA, Asanuma H. Information processing within the motor cortex. II. Intracortical connections between neurons receiving somatosensory cortical input and motor output neurons of the cortex. J Comp Neurol. 1994;345: 172-184.

53. Soekadar SR, Witkowski M, Birbaumer N, Cohen LG. Enhancing Hebbian Learning to Control Brain Oscillatory Activity. Cereb Cortex. 2014.

54. Joundi RA, Jenkinson N, Brittain JS, Aziz TZ, Brown P. Driving oscillatory activity in the human cortex enhances motor performance. Curr Biol. 2012;22: 403-407.

55. Jones EG, Coulter JD, Hendry SH. Intracortical connectivity of architectonic fields in the somatic sensory, motor and parietal cortex of monkeys. J Comp Neurol. 1978;181: 291-347.

56. Farkas T, Kis Z, Toldi J, Wolff J-. Activation of the primary motor cortex by somatosensory stimulation in adult rats is mediated mainly by associational connections from the somatosensory cortex. Neuroscience. 1999;90: 353-361.

57. Beekhuizen KS, Field-Fote EC. Massed practice versus massed practice with stimulation: effects on upper extremity function and cortical plasticity in individuals with incomplete cervical spinal cord injury. Neurorehabil Neural Repair. 2005;19: 33-45.

58. Beekhuizen KS, Field-Fote EC. Sensory stimulation augments the effects of massed practice training in persons with tetraplegia. Arch Phys Med Rehabil. 2008;89: 602-608.

59. Ziemann U, Muellbacher W, Hallett M, Cohen LG. Modulation of practice-dependent plasticity in human motor cortex. Brain. 2001;124: 1171-1181.

60. Muellbacher W, Ziemann U, Boroojerdi B, Cohen L, Hallett M. Role of the human motor cortex in rapid motor learning. Exp Brain Res. 2001;136: 431-438.

61. Butefisch CM, Davis BC, Wise SP, Sawaki L, Kopylev L, Classen J, et al. Mechanisms of use-dependent plasticity in the human motor cortex. Proc Natl Acad Sci U S A. 2000;97: 3661-3665.

62. Classen J, Liepert J, Wise SP, Hallett M, Cohen LG. Rapid plasticity of human cortical movement representation induced by practice. J Neurophysiol. 1998;79: 1117-1123.

63. Shemmell J, Riek S, Tresilian JR, Carson RG. The role of the primary motor cortex during skill acquisition on a two-degrees-of-freedom movement task. J Mot Behav. 2007;39: 29-39.

64. Carroll TJ, Lee M, Hsu M, Sayde J. Unilateral practice of a ballistic movement causes bilateral increases in performance and corticospinal excitability. J Appl Physiol (1985). 2008;104: 1656-1664.

65. Perez MA, Wise SP, Willingham DT, Cohen LG. Neurophysiological mechanisms involved in transfer of procedural knowledge. J Neurosci. 2007;27: 1045-1053.

66. Baraduc P, Lang N, Rothwell JC, Wolpert DM. Consolidation of Dynamic Motor Learning Is Not Disrupted by rTMS of Primary Motor Cortex. Current Biology. 2004;14: 252-256.

67. Hamdy S, Rothwell JC, Aziz Q, Singh KD, Thompson DG. Long-term reorganization of human motor cortex driven by short-term sensory stimulation. Nat Neurosci. 1998;1: 64-68.

68. Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J. Induction of plasticity in the human motor cortex by paired associative stimulation. Brain. 2000;123 Pt 3: 572-584.

69. Ridding MC, Taylor JL. Mechanisms of motor-evoked potential facilitation following prolonged dual peripheral and central stimulation in humans. J Physiol. 2001;537: 623-631.

70. Smyth C, Summers JJ, Garry MI. Differences in motor learning success are associated with differences in M1 excitability. Hum Mov Sci. 2010;29: 618-630.

71. Garry MI, Kamen G, Nordstrom MA. Hemispheric differences in the relationship between corticomotor excitability changes following a fine-motor task and motor learning. J Neurophysiol. 2004;91: 1570-1578.

72. Gallasch E, Christova M, Krenn M, Kossev A, Rafolt D. Changes in motor cortex excitability following training of a novel goal-directed motor task. Eur J Appl Physiol. 2009;105: 47-54.

73. Hess G, Donoghue JP. Long-term potentiation and long-term depression of horizontal connections in rat motor cortex. Acta Neurobiol Exp (Wars). 1996;56: 397-405.

74. Murase N, Cengiz B, Rothwell JC. Inter-individual Variation in the After-effect of Paired Associative Stimulation can be Predicted From Short-interval Intracortical Inhibition With the Threshold Tracking Method. Brain Stimul. 2015;8: 105-113.

75. Jacobs M, Premji A, Nelson AJ. Plasticity-inducing TMS protocols to investigate somatosensory control of hand function. Neural Plast. 2012;2012: 350574.

76. Seidler RD, Bernard JA, Burutolu TB, Fling BW, Gordon MT, Gwin JT, et al. Motor control and aging: links to age-related brain structural, functional, and biochemical effects. Neurosci Biobehav Rev. 2010;34: 721-733.

77. Camus M, Ragert P, Vandermeeren Y, Cohen LG. Mechanisms controlling motor output to a transfer hand after learning a sequential pinch force skill with the opposite hand. Clin Neurophysiol. 2009;120: 1859-1865.

78. Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W. Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. Ann Neurol. 1996;40: 367-378.

79. Uehara K, Morishita T, Kubota S, Funase K. Neural mechanisms underlying the changes in ipsilateral primary motor cortex excitability during unilateral rhythmic muscle contraction. Behav Brain Res. 2013;240: 33-45.

80. Hiraoka K, Ae M, Ogura N, Sano C, Shiomi K, Morita Y, et al. Bimanual coordination of force enhances interhemispheric inhibition between the primary motor cortices. Neuroreport. 2014;25: 1203-1207.

81. Hortobagyi T, Richardson SP, Lomarev M, Shamim E, Meunier S, Russman H, et al. Interhemispheric plasticity in humans. Med Sci Sports Exerc. 2011;43: 1188-1199.

82. Garvey MA, Ziemann U, Becker DA, Barker CA, Bartko JJ. New graphical method to measure silent periods evoked by transcranial magnetic stimulation. Clin Neurophysiol. 2001;112: 1451-1460.

83. Perez MA, Butler JE, Taylor JL. Modulation of transcallosal inhibition by bilateral activation of agonist and antagonist proximal arm muscles. J Neurophysiol. 2014;111: 405-414.

84. Giovannelli F, Borgheresi A, Balestrieri F, Zaccara G, Viggiano MP, Cincotta M, et al. Modulation of interhemispheric inhibition by volitional motor activity: an ipsilateral silent period study. J Physiol. 2009;587: 5393-5410.

85. Schulte T, Muller-Oehring EM. Contribution of callosal connections to the interhemispheric integration of visuomotor and cognitive processes. Neuropsychol Rev. 2010;20: 174-190.

86. Chipchase LS, Schabrun SM, Hodges PW. Corticospinal excitability is dependent on the parameters of peripheral electric stimulation: a preliminary study. Arch Phys Med Rehabil. 2011;92: 1423-1430.

87. Schabrun SM, Ridding MC, Galea MP, Hodges PW, Chipchase LS. Primary sensory and motor cortex excitability are co-modulated in response to peripheral electrical nerve stimulation. PLoS One. 2012;7: e51298.

88. Nielsen JB. Sensorimotor integration at spinal level as a basis for muscle coordination during voluntary movement in humans. J Appl Physiol (1985). 2004;96: 1961-1967.

89. Poh E, Riek S, Carroll TJ. Ipsilateral corticospinal responses to ballistic training are similar for various intensities and timings of TMS. Acta Physiol (Oxf). 2013;207: 385-396.